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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	John L. Schenk
Serial Number:	09/478,299
Filed:	January 5, 2000
Parent Title:	Method of Cryopreserving Selected Sperm Cells
Group Art Unit:	1651
Examiner:	M. Meller
Assignee:	XY, Inc.

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. §1.192

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

REAL PARTY IN INTEREST

The subject application is owned by XY, Inc. whose current address is Moondrift Ranch, 1108 North Lemay Avenue, Fort Collins, Colorado 80524, U.S.A., a Colorado Corporation.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

On March 7, 2002, appellant appealed from the final rejections of claims 1-26 and 35. Claims 27-34 and claims 36 and 37 were cancelled without prejudice in appellant's response to the official communication mailed April 12, 2000 pursuant to a restriction requirement.

STATUS OF AMENDMENTS

Claims 1-26, and 35 have not been amended during examination of the application. Hence, claims 1-26 and 35 are in the form as originally filed.

SUMMARY OF THE INVENTION

Appellant's invention comprises a method of cryopreservation of sperm cells that have been selected for a particular characteristic and the corresponding frozen sperm cells selected for a particular characteristic that are fertile and can be successfully used for artificial insemination in vivo to achieve pregnancies or for in vitro fertilization to produce embryos.

The examiner imposed a restriction requirement that included the method of cryopreservation of sperm cells that have been selected for a particular characteristic and a product by that method in a first group (Group I, claims 1-26 and 35); the frozen sperm

selected for a particular characteristic in a second group (Group II, claims 27-34); and the method of using the product in a third group (Group III, claims 36 and 37). The examiner further imposed an election of species requirement that necessitated election of one of the patentably distinct species set out by claim 12 and requiring the applicant to identify one specific cryoprotectant and one specific additional component. Group I was elected, and that is the group on appeal. The elected claims in Group I, are set forth in Appendix B to this brief.

Appellant's method of freezing sperm cells that have been selected for a particular characteristic (claims 1-26) and a product by such method (claim 35) (comprising elected Group I), provides selected frozen sperm cells that when thawed can be used to successfully inseminate a female mammals and achieve pregnancies or used in vitro for fertilization of oocytes. Specification at page 3, lines 9-12. Selected sperm cells comprise sperm cells isolated from the normal population of sperm cells in ejaculates of male mammals based upon the presence or absence of a specific characteristic. Specification at page 3, lines 9-10 and page 4, lines 9-10. Thus, a selected sperm sample is obtained by subjecting the normal sperm cell population in an ejaculate of a male mammal to selection for a specific characteristic. Specification at p. 4, lines 11-12. A selected sperm sample is therefore enriched in the characteristic selected for, relative to the normal sperm cell population in an ejaculate of a male mammal. Specification at p. 4, lines 12-13. Selected sperm samples are then frozen. Specification at page 3, lines 9-10. Thawing of frozen selected sperm cells yields viable sperm that can be used in procedures such as artificial insemination and in vitro fertilization. Specification at page 3, lines 11-12.

The various embodiments of the invention can further include frozen selected sperm cells that have a concentration of frozen selected sperm cells that is lower than the concentration of normal populations of sperm cells in ejaculates. Specification at page 15, lines 24-28, Claim 2. The concentration of frozen selected sperm cells with respect to some embodiments of the invention can be about 1 x 10^6/mL to about 300 x 10^6/mL. Specification at page 11, lines 25-26.

The various embodiments of the invention can further include, sex-selecting frozen sperm cells to establish either enriched X-chromosome bearing or Y-chromosome bearing populations as compared to normal sperm cell populations of ejaculates. Specification at page 5, lines 25-30, page 6, lines 1-6; Claim 3. The sperm cells contained in ejaculates of various mammals, including, but not limited to, bovine sperm cells, equine sperm cells, porcine sperm cells, ovine sperm cells, elk sperm cells, or bison sperm cells can be sex-selected. Specification at page 5, lines 13-17; Claims 4-7. Various procedures can be used to sex-select sperm cells obtained from such male mammals including but not limited to magnetic techniques, gravimetric techniques, biochemical techniques, sperm cell motility techniques among others described. Specification at page 5, lines 25-31 and page 6, lines 6; Claim 8. The invention further specifically includes freezing of sex-selected cells obtained by flow sorting of sperm cells contained in ejaculates by flow cytometery. Specification at page 6, lines 7-19; Claim 9.

The various embodiments of the invention further include cooling of frozen selected sperm cells at 5° degrees Celsius prior to freezing. Specification at page 10, lines 26-28; Claim 10. Suitable conditions for cooling of selected sperm cells can comprise an extended cooling period of between about 60 minutes to about 240 minutes. Specification at page 10, lines 29-31, page 11, lines 1-3; Claim 11.

Embodiments of the invention can further comprise adding a final extender to selected sperm cells that contains a cryoprotectant compatible with selected sperm cell to be frozen, such as, glycerol, dimethyl sulfoxide, ehtylene glycol, or propylene glycol. Specification at page 8, lines 4-14; Claim 14.

Embodiments of the invention can further comprise adding a final extender to selected sperm samples that contains, in addition to a cryoprotectant, one or more of the following components: a component that maintains osmolality and buffers pH, an organic substance that reduces cold shock and preserves fertility of sperm, an energy source, a substance that facilitates sperm capacitation, and an antibiotic. Claim 12. Osmolality and pH can be maintained by establishing a buffer containing a salt, a carbohydrate, or specifically Tris[hydroxmethyl]aminomethane, and TES (N-Tris [hydroxmethyl]methyl-2-aminomethanesulfonic acid), and monosodium glutamate buffers; milk; or HEPES-buffered medium. Specification at page 8, lines 26; Claims 15 and 16. Cold shock can be reduced and fertility of sperm preserved using organic substances such as lipoproteins, phospholipids, lecithin, egg yolk, egg yolk extract, milk, milk extract, casein, albumin, or a detergent such as sodium dodecyl sulfate. Specification at page 9, lines 5-7; Claim 17.

Energy sources that can be readily utilized by selected sperm cells can include for example sugars such as monossaccharides, disaccharides, trisaccharides, glucose, fructiose, or mannose. Specification at page 9, lines 17-23; Claims 13, 14, and 18. Substances that facilitate sperm capacitation can be enzymes such as alpha amylase, beta amylase, beta glucuronidase. Specification at page 9, lines 29-30, page 10, lines1-2. Antibiotics such as tylosin, gentamicin, lincomycin, spectinomycin, linco-spectin, penicillin, streptomycin, ticarcillin although any variety of antibiotics or combinations thereof compatible with the species of selected sperm cell can be used. Specification at page 10, lines 6-10.

As to some embodiments of the invention, isolating selected sperm cells from the selected sperm sample in initial extender can be accomplished by centrifugation. Specification at p. 11, lines 6 and 13; Claim 24. Centrifugation in accordance with the invention can isolate at least 50% to about 90% if the selected sperm cells in the selected sperm sample. Specification page 11, line 17; Claim 25.

Certain embodiments of the invention can further provide frozen selected sperm cells in an final extender has a pH range of about 6.5 to about 7.5. Claim23

Certain embodiments of the invention provide a suspension of selected sperm cells in a mixture prior to freezing of glycerol, sodium citrate, Tris[hydroxymethyl]aminomethane, egg yolk, fructose, and one or more antibiotics.

Specification at page 12, lines3-7; page 13, table entitled "Components of Egg Yolk-Tris Extender"; Claim 20.

Other embodiments of the invention provide a suspension of selected sperm cells in a mixture prior to freezing of glycerol, sodium citrate, egg yolk, and one or more antibiotics. Specification at page 13, lines 18-22; page 14, table entitled "Components of Egg-Citrate Extender"; Claim 21.

Another embodiment of the invention provides a suspension of selected sperm cells in a mixture prior to freezing of glycerol, heated homogenized milk, fructose, and one or more antibiotics. Specification at page 15, lines 17-21; page 16, table entitled Components of Milk Extender; Claim 22.

Importantly, the inventors have demonstrated, for the first time, that frozen selected sperm cell products resulting from the various embodiments of the invention can be thawed and used to inseminate female mammals and successfully achieve pregnancies or used for in vitro for fertilization of oocytes. Specification at page 3, lines 9-12. The ability to freeze selected sperm cells, which the invention provides, will enable widespread use of selected sperm cells. Specification page 3, llies 22-24. As such, the invention represents an important advance in livestock management, where selection of sperm cells for use in such procedures can be used to increase the production of offspring having desirable traits. Specification at page 3, lines 17-19.

ISSUES

1. Whether the examiner incorrectly rejected the claims 1 and 35 under Section 112, second paragraph, as being indefinite and failing to particularly point out and distinctly define the metes and bounds of the invention?

2. Whether the examiner incorrectly rejected claims 1-26 and 35 under 35 U.S.C. §103(a) as unpatentable over Salisbury et al, Physiology of Reproduction and Artificial Insemination of Cattle, 2nd Ed., San Francisco: W. H. Freeman, 442-554 (1978) in view of United States Patent No. 5,021,244, issued on June 4, 1991, to Spaulding.

GROUPING OF CLAIMS

Claims 1-26 and 35 stand or fall together.

EXAMINER'S RATIONALE

The examiner's rational for rejecting claims 1-26 and 35 as unpatentable over Salisbury et al, Physiology of Reproduction and Artificial Insemination of Cattle, 2nd Ed., San Francisco: W. H. Freeman, 442-554 (1978) in view of United States Patent No. 5,021,244, issued on June 4, 1991, to Spaulding was stated in his first office action as follows:

"Claims 1-26 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 35, step c) which calls for "isolating sperm from said selected sperm sample to produce isolated sperm", is confusing since a sperm sample is isolated

once it is no longer in the testicles. Step c, is thus redundant in its recitation of "isolating sperm" since the sperm is already isolated.

Further, the claim is confusing since the term, "final extender" is confusing. What is the final extender final to? There is no beginning extender." and;

"Claims 1-26 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salisbury et al. taken with Spauding.

The claims are drawn to a method for the cryopreservation of sperm as in claims 1 and 35 using an extender the elected extender containing glycerol and a component that maintains osmolality and buffers pH.

Salisbury teaches cryopreservation of bull semen using different extenders including glycerol (page 487) and a component that maintains osmolality and buffers pH as sodium citrate, Tris, milk, etc. Salisbury also teaches obtaining the sperm cooling it to 5 C for 140 minutes (see page 475-see also pages 463-464 for additional cooling semen), adding the extender (see page 456, 499), and freezing the suspension of sperm (see pages 471, 494, 495, 503-504). The pH of the extender is 6.5 to 7.0 (page 502 and page 456). See entire reference especially pages mentioned.

Salisbury does not teach to specifically isolate the sperm using centrifugation and does not teach using flow cytometry to select the sperm sample.

Spalding teaches to sort sperm for their X or Y characteristic, by flow cytometry and to centrifuge sperm cells to remove seminal proteins, i.e. isolate the sperm, after cooling, see example 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use flow cytometery to select sperm for a particular characteristic in the method of Salisbury since Spaulding teaches using flow cytometry to sort X from Y sperm. To centrifuge (isolate) the sperm sample of Salisbury after cooling would have been obvious since Spaulding teaches to remove seminal plasma proteins, i.e. isolate the sperm after cooling.

Since Salisbury uses bull sperm it also would have been obvious to use other mammalian sperm such as equine and porcine since they are also mammalian sperm and would be expected to work well within the purview of the skilled artisan.

A 50% to 90% recovery of sperm from the centrifugation is obvious since one would want to yield as much of the sperm possible.

The concentration of sperm in said suspension prior to freezing would be inherent to the suspension of sperm.

The order of the steps of the process of Salisbury might be out of order from the claimed process, but this is still obvious. MPEP 2144.04 IV (C) states that it is prima facie obvious to perform in any order steps of a process.

Thus, the claimed subject matter is obvious over the cited references."

The examiner's rational for rejecting claims 1-26 and as unpatentable over Salisbury et al, Physiology of Reproduction and Artificial Insemination of Cattle, 2nd Ed., San Francisco: W. H. Freeman, 442-554 (1978) in view of United States Patent No. 5,021,244, issued on June 4, 1991, to Spaulding was further set forth in the final rejection as follows:

> "Applicants argue that Salisbury does not teach or suggest that sperm selected for a particular characteristic may be frozen or that pregnancies can be achieved with such selected cryopreserved sperm. In response to applicants arguments against the references individually, one cannot show nonobviousness by attacking the references individually where the rejections are based on a combination of references. See *In Re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In Re Merck &Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).
>
> Applicant cannot expect Salisbury to contain all the elements of the claims since Salisbury was used in a 35 USC 103 rejection taken with Spaulding.
>
> Further, Salisbury does teach freezing of sperm and Spaulding teaches the selection of the sperm for a particular characteristic, namely, sex.
>
> Also, the elected claims are not directed to pregnancies resulting from the use of the sperm, thus this argument by the applicant is moot.
>
> Thus, the claimed subject matter is properly rejected under this section."

ARGUMENT

I. Claims 1 and 35 Should Not Have Been Rejected Under Section 112 Second Paragraph As They Are Sufficiently Definite And Particularly Point Out And Distinctly Define The Metes And Bounds Of The Invention.

The applicant believes that the claims as recited are both definite and particular point out and distinctly define the metes and bounds of the invent as required under 35 U.S.C. §112, second paragraph.

Section 112, second paragraph sets out two separate requirements:

"(A) the claims must set forth the subject matter that applicants regard as their invention; and

(B) the claims must particularly poihtout and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant."

In satisfying the requirements of §112, the meaning of words used in a claim are not to be construed in a "lexicographic vacuum, but in the context of the specification and drawings. MPEP §2106(C). "An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation as it is used in the claim." MPEP §2106(C); Toro Col v White Consolidated, 199 F.3d 1295, 1301, 53 USPQ 1065, 1069 (Fed. Cir. 1999) (emphasis added). Office personnel must rely on the applicant's disclosure to properly determine the meaning of the terms used in the claims. MPEP §2106 (C); Markman v. West view Instruments, 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir.)(en banc), aff'd 116 S.Ct. 1384 (1996).

If a rejection is based on §112, second paragraph, the examiner should further explain whether the rejection is based on indefiniteness or on the failure to claim what applicants regard as their invention. MPEP §2171; Ex parte Ionescu, 222 USPQ 537, 539 (Bd. App. 1984).

In the instant case the examiner indicates that the claims are rejected under §112 "as being indefinite for failing to particularly point out and distinctly claim the subject matter of which the applicant regards as the invention." Office Action Summary, page 3, item 3. It appears to the appellant that the examiner has combined concerns regarding "indefiniteness" and the "failure to claim what applicants regard as there invention" to the extent that the applicant could not reasonably understand which concern to address. Id. As a matter of convenience for the Board the applicant will address both as follows:

The examiner expressed the concern that in "claim 1 and 35, step c) which calls for 'isolating sperm from said selected sperm sample to produce isolated sperm is confusing." Office Action Summary mailed December 19, 2000, page 3, item 3.

In the specification under the heading entitled "Isolation of Sperm Cells from the Selected Sperm Sample" the appellant provides an explicit definition of the term "isolation" as meaning "after initial extension of the selected sperm, sperm are isolated from the sample using any sufficiently gentle isolation method that provides at least 50% recovery of sperm. ..". Specification at page 11, lines 5-8. The applicant further provides

an explicit definition of the term "initial extender" as "a medium used to extend sperm prior to isolation step of the method of this invention". Specification at page 4, lines18-19. The applicant further provides detailed examples of "a variety of methods suitable for recovering cells from suspension to isolate sperm. Specification page 11, starting at line 12. These examples include for example, "filtration, sedimentation, and centrifugation. . . In an exemplary preferred embodiment, the selected sperm is aliquoted into 50 ml tubes at volumes not exceeding 27ml. . .the centrifugation step provides at least about 50%. . .recovery of sperm. . .After isolation, the supernatant is removed and the pellet is suspended by vortexing gently. . .. Specification at page 11, lines 13-20.

Because appellant has acted as his own lexicographer and explicitly defined the term "isolating sperm" in the specification in a manner which would be apparent to any person of ordinary skill in the art at the time the invention was made as to what the appellant regards as his invention, and also particularly points and distinctly defines the metes and bounds of the subject matter to be protected by the patent grant, and because appellant's definition is not repugnant to the usual meaning of the term, appellants definition of the term should be allowed to control the interpretation of the claims and should not have been rejected by the examiner. Certainly, no person of ordinary skill in the art would interpret "isolating sperm" as the examiner suggests "a sperm sample is isolated once it is no longer in the testicles."

The examiner also rejected under §112, second paragraph, the term "final extender" as "confusing". Office Action Summary mailed December 19, 2000, page 3,

item 3. In the Specification, under the heading "Definitions" the appellant has explicitly defined both "initial extender" as meaning "a medium used to extend sperm prior to the isolation step of the method of this invention" and "final extender" as "a medium used to extend sperm prior to the freezing step of the method of the invention". Specification page 4, lines 18-21. Additionally, in the specification under the heading "Final Extension of Isolated Sperm Cells" the appellant clearly indicates that "After isolation, the sperm are pooled. . .and extended with final extender to an appropriate concentration for freezing." Specification at page 11, lines23-25. The appellant then provides various types of suitable final extenders as examples. Specification at page 11, line 29 through page 16, line 21.

Again, because appellant has acted as his own lexicographer and explicitly defined the terms "initial extender" and "final extender" in the specification in a manner which would be apparent to any person of ordinary skill in the art at the time the invention was made as to what the appellant regards as his invention, and also particularly points and distinctly defines the metes and bounds of the subject matter to be protected by the patent grant, and because appellant's definition is not repugnant to the usual meaning of the term, appellants definition of the term should be allowed to control the interpretation of the claims and should not have been rejected by the examiner.

Moreover, the appellant selected both terms "isolating sperm" and "final extender" as generic terms to include the wide variation in the manner of isolating sperm,

and to further include the numerous compositions of final extenders described in the specification and which can be used with the invention.

The appellant respectfully requests that the Board reverse the examiner's rejection allowing the appellant to retain the terms "isolating sperm" and "final extender" as originally recited in the specification as filed because they meet both standards set by §112, second paragraph, and provide appellant with the breadth of claim scope that fairly represents his invention.

II. The Examiner Has Not Established A Case of Obviousness Under Section 103 By Rejection Of Claims 1-26 and 35 As Unpatentable Over Salisbury et al. In View Of Spaulding.

The appellant believes that the examiner has not established a prima facie case of obviousness with respect to the appellant's claimed method of cryopreserving sperm using the combination of Salisbury et al, Physiology of Reproduction and Artificial Insemination of Cattle, 2nd Ed., San Francisco: W. H. Freeman, 442-554 (1978) (Salisbury) in view of United States Patent No. 5,021,244, issued on June 4, 1991, to Spaulding (Spaulding).

A prima facie case of obviousness requires that the references in combination teach or suggest all the claim limitations; there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill of the art to modify the reference or combine reference teachings; and there

must be a reasonable expectation of success. §2143, MPEP; In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, the combination of references does not teach or suggest all the limitations of the claimed invention as required. §2143, MPEP; §2143.03, MPEP; In re Royka, 490 F.2d 981 (CCPA 1974).

In this regard, with respect to claims 1 and 35, the examiner has failed to use the appellant's explicit definition of the term "sperm" set out in the specification, as required under the rules. As discussed at length by appellant above, "office personnel must rely on the applicant's disclosure to properly determine the meaning of the terms used in the claims. MPEP §2106 (C); Markman v. West view Instruments, 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir.)(en banc), aff'd 116 S.Ct. 1384 (1996). "An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation as it is used in the claim." MPEP, §2106(C); Toro Co. v. White Consolidated, 199 F.3d 1295, 1301, 53 USPQ 1065, 1069 (Fed. Cir. 1999) (emphasis added).

The applicant has explicitly defined the term "sperm" as used in claim one to mean "fertile sperm". Specification at page 3, lines 11-12; Appellants Response Under 37 C.F.R. §1.111 at page 2, ¶4. As can be explicitly understood from the specification and appellant's response to the office's first action, "The present inventors have

demonstrated, for the first time, that pregnancies can be achieved with sperm that has been selected and then frozen." Specification at page 3, lines 15-16 (emphasis added). "The present invention allows cryopreservation of sperm that have been selected for a particular characteristic. . .Thawing yields viable sperm that can be used in procedures such as artificial insemination and in vitro fertilization." Specification at page 3, lines9-12.

The examiner, in order to make the combination of references teach each element of claim 1, impermissibly broadens appellant's explicit definition of "selected sperm sample" to include the products taught by Spaulding regardless of the fact that there is no evidence within the combination of references that these products include any "viable sperm" which could be used to fertilize a female mammal to achieve pregnancies.

The Salisbury reference cited by the examiner makes it unequivocally clear why the appellant's explicit definition of "selected sperm sample" and evidence of pregnancies is necessary in understanding the meaning and scope of claim 1:

"Spermatozoa must be alive to be fertile. . .and motility has been used to monitor viability. Motility, however, is primarily a reflection of flagellar activity, and it does not guarantee that such cells are fertile. The integrity of the genetic material in the sperm chromatin must also be preserved in order for normal embryo development to take place after fertilization. . .there is no test of semen quality prior to use that can predict how well the genetic material is maintained."

Salisbury at page 442.

When the explicit definition set out by the appellant in the specification and claim 1 is properly interpreted it can be understood that the combination of references do not at teach the claimed limitation of "selected sperm cells" of the invention because Salisbury does not teach "selected sperm cells" at all and not a single pregnancy can be attributed to the technology described by Spaulding. This is not surprising in that although the combined references are 132 pages in length there is only a two sentence description of any application of freezing to any type of selected sperm cells and there is no evidence any of the selected sperm cells are fertile selected sperm cells. Spaulding, col. 18, lines30-34. As can be understood, the Spaulding reference carefully avoids any indication what-so-ever that the mixture of sperm cells modified with X- or Y- SAM proteins can actually fertilize an egg or that any pregnancy can be achieved. As such, there is no indication that the appellant's definition of "sperm" which is limited to frozen selected fertile sperm cells includes any of the sperm cells described in the combination of references.

Because the none of the references in the combination of Salisbury et al. in view of Spaulding disclose, teach, or suggest the claimed limitation of "selected sperm cells" as explicitly defined in the specification as being fertile, a prima facie case of obviousness cannot be established with regard to the claim limitations in claim 1, nor any claim depending there from. § 2143.03, MPEP; In re Fine, 837 F.2d 1071 (Fed. Cir. 1988).

As such, respectfully request that the examiners rejection of claims 1-27 and 35 be reversed and claims 1-26 and 35 should have been allowed as originally recited, or amended to further clarify fertile sperm cells.

Secondly, the references do not provide the requisite suggestion or motivation to combine the references as required by § 2143.01, MPEP. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the claimed invention. §2143.01, MPEP; In Re Mills, 916 F.2d 680 (Fed. Cir. 1990).

As the examiner indicates the "Salisbury reference it teaches cryopreservation of bull semen using different extenders." Office Action Summary mailed December 19, 2000 at page 4, item 5 (emphasis added). The examiner points out that "Salisbury does not teach to specifically isolate the sperm using centrifugation and does not teach flow cytometry to select the sperm sample." Office Action Summary mailed December 19, 2000 at page 4, item 5.

Importantly, the examiner omits to point out that Salisbury the primary reference does not teach the first element of appellants invention "obtaining a selected sperm sample". Claim 1, element a. This is an important difference because "selected sperm samples" are "obtained by subjecting a source sample to selection based on a specific

characteristic." Specification at page 4, lines 9-13. As such, the Salisbury reference does not teach any of the elements of the claimed invention:

"a. obtaining a selected sperm sample;

b. cooling said selected sperm sample;

c. isolating sperm from said selected sperm sample;

d. adding final extender to said isolated sperm to produce a suspension of sperm; and

e. freezing said suspension of sperm."

Claim 1, Specification at page 55. (emphasis underline added to highlight that "selected sperm" not semen or sperm cells contained within semen are the subject matter of the claimed invention).

There is no relationship what-so-ever between semen, or sperm cells contained within semen, as taught by Salisbury to the "selected sperm cells" which are used in accordance with the invention. First, it is apparent from the specification that "selected sperm cells" are not a natural product; selected sperm cells are removed from the seminal plasma; selected by a characteristic to establish a non-naturally occurring population of sperm cells purified for a particular characteristic (specification at page 4, ll. 9-15, including but not limited to sex-selected sperm, specification at page 17, ll. 19-25); can contain a variety of components besides selected sperm cells (specification page 7, ll. 7); and may as a consequence of the selection process be modified to the extent that they are not sperm cells in the conventional sense, at all (specification at page 5, lines 9-15; page 17, lines 19-25; page 6, lines 7-19) (describing stain bound to DNA of selected sperm

cells obtained by flow cytometry). As such, the Salisbury reference does not disclose any limitation of the invention (and arguably is not even a pertinent reference given that the reference itself indicates that it is "impossible to generalize findings" as "one set of conditions may not be acceptable for others"). Salisbury at page 499. As such, within the combination of references the examiner must rely upon the Spaulding reference to show that limitations of the invention were taught, and to provide a suggestion that it can be combined at all with the Salisbury reference.

The Spaulding reference focuses on producing a "polyclonal or monoclonal antibodies. . . useful to modify mammalian semen." Spaulding, col. 17, ll. 61-62. "When incubated with a semen sample. . .Sperm bound with antibodies become inactivated--their mobility is impeded." Spaulding, col. 17, ll. 67-68, col. 18, l. 1 (emphasis added to highlight that Spaulding obtains semen not selected sperm cells). "The semen was either collected and frozen in liquid nitrogen, or it may be freshly ejaculated." Spaulding, col. 18, ll. 15-16. "antibodies are incubated with the semen sample for 15-60 min at 37 C. Following incubation, the mixture is used directly for artificial insemination (AI) or is frozen in liquid nitrogen according to standard procedures." Spaulding, col. 18, ll. 30-34. As can be understood, in the entire Spaulding reference the indication that " or is frozen in liquid nitrogen according to standard procedures" is the only reference to any freezing step. Spaulding col. 18, 33-34. However, in combination with Salisbury this singular statement does not suggest the desirability of the claimed invention.

The mere fact that the references can be combined or that the combination could be modified does not render the invention obvious unless the references also suggest the desirability of the invention. MPEP, §2143.01; In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)("Although a prior art device may be capable of being modified. . .there must be a suggestion or motivation in the reference to do so." Id at 682, 1432). The combination of Salisbury and Spaulding do not teach freezing of "selected sperm cells" removed from the seminal plasma. Moreover, Spaulding does not suggest in any manner that freezing of semen as taught by Salisbury, or any conventional freezing technology for that matter, should be modified to operate with "selected sperm cells" which are removed from the seminal plasma.

The examiner further argues that because "Spaulding teaches to sort sperm for their X or Y characteristics, by flow cytometry and to centrifuge sperm cells to remove seminal proteins, i.e. isolate the sperm, after cooling . . .It would have been obvious to one of ordinary skill in the art at the time the invention was made to use flow cytometery to select sperm for a particular characteristic in the method of Salisbury since Spaulding teaches flow cytometry to sort X from Y sperm. To centrifuge (isolate) the sperm sample of Salisbury after cooling would have been obvious since Spaulding teaches to remove seminal plasma proteins, i.e. isolate the sperm after cooling. Office Action Summary mailed December 19, 2000 at page 5, item 5.

However, the examiners argument amounts to nothing more than a statement that flow sorting of stained sperm cells and centrifugation of flow sorted sperm cells was

known in the art, bald of any objective reason to combine the teaching with the prior art. The fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a prima facie case of obviousness. MPEP, §2143.01; Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Interfer. 1993).

Spaulding does not teach, nor does it suggest that, sorted sperm cells (or any selected sperm cells which are isolated), can be frozen for any purpose. Spaulding collected subpopulations of sperm cells by flow cytometry "for isolation and identification of the novel, enriched plasma membrane vesicles and the SAM proteins. . .." Spaulding, col. 10, ll. 3-5. "We cavitated cell samples containing enriched X-sperm or Y-sperm populations in Parr bombs." Spaulding, col. 10, ll. 18-19.

With respect to claims 5-7, having limitations which are not disclosed by either reference as discussed above, the examiner attempts to dispose of these limitations in a similar fashion by merely indicating that "equine and porcine since they are also mammalian sperm . . . would be expected to work well with the purview of the skilled artisan." . Office Action Summary mailed December 19, 2000 at page 5, item 5. Again, this argument is nothing more an argument that it was well within the skill of the art which is not sufficient by itself to establish a prima facie case of obviousness. MPEP, §2143.01; Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Interfer. 1993).

With respect, to claim 25, the examiner again uses the impermissible "well within the ordinary skill of the art" argument that "a 50% to 90% recovery of sperm from the centrifugation is obvious since one would want to yield as much sperm as possible.

With respect to claims 2 and 26, the examiner urges that the concentration of the suspension of cells claimed would be "inherent" to the suspension itself. However, freezing this concentration of "selected sperm cells" is not taught by either reference and there is no suggestion in the Spaulding reference to apply the teaching of Salisbury to that concentration of selected sperm cells. To the contrary, the teaching of Salisbury conflicts with any attempt to combine the references and would render the Salisbury reference inoperable. "In New Zealand, . . . when frozen semen has been banked. . .the semen is thawed and reconstituted. . . with 20 million sperm per dose." Salisbury p. 475.

With respect to claim 23, the pH of the extender claimed by appellant for selected sperm cells is not used either by Spaulding or Salisbury for freezing selected sperm cells and Spaulding does not suggest that the teachings of Salisbury should apply to isolated selected sperm cells.

Because the references in the combination of Salisbury et al. in view of Spaulding do not provide the requisite motivation or suggestion for combination a prima facie case of obviousness cannot be established with regard to the claim limitations in claim 1, nor any claim depending there from. § 2143.03, MPEP; In re Fine, 837 F.2d 1071 (Fed. Cir. 1988).

As such, respectfully request that the examiners rejection of claims 1-27 and 35 be reversed and claims 1-26 and 35 be allowed as originally recited, or amended to further clarify fertile sperm cells.

Fourth, the combination of references does not provide one of ordinary skill in the art a reasonable expectation of successfully making the invention at the time the invention was made. §2143.02, MPEP. Where the references provide only a general approach as to the particular form of the claimed invention or how to achieve it, the invention is not obvious, but only obvious -to-try. In Re O'Farrell, 853 F. 2d 894, 903 (Fed. Cir. 1988).

With respect to claims 1-26 and 35, the teaching described by Salisbury does not provide any description of how to make, isolate, or freeze the "selected sperm cells" claimed by the appellant in claims 1-26 and 35. It only provides teachings as to how to freeze semen which comes with a variety of disclaimers and warnings that "the exact nature of freeze thaw damage is not fully understood" (page 497); that "factors in seminal processing make it impossible to generalize these findings (page 499); there is no test for semen quality prior to use that can predict how well the genetic material is maintained (page 442) and so forth. The Spaulding reference does not provide any description of how to freeze isolated selected sperm cells because the few sperm cells that represented isolated selected subpopulations were destroyed by cavitation and not frozen at all. Spaulding, col. 10, ll. 18-19. The only description in Salisbury pertains to sperm cells in

seminal plasma and to freeze these sperm cells "according to standard procedures". Spaulding, col. 18, ll. 33-34. This provides nothing more than is offered by Salisbury (which are standard procedures) which does not address any aspect of freezing with regard to selected sperm cells as claimed by appellant and comes with all the admonitions of Spaulding that it may not work as to any given set of circumstances.

Specifically with respect to claims 2 and 26, there is no description at all of freezing selected sperm cells at a concentration lower than in the source sample or in the range of 1 x 10 6/ ml to about 300 x 10 6/ ml. This range being important to the appellant because selected sperm cells are scarce; while it was unimportant when nearly unlimited sperm cells are available when freezing semen. Moreover, again the Salisbury reference indicates that "dilution of the spermatozoa with simple solutions depresses motility". Salisbury at page 446; See also specification at page 22, ll. 30-31 (high sperm dilution and cooling resulted in a substantial reduction in the percentage of motile sperm. . .this was greatly attenuated by concentrating the diluted sperm to 10 x 10 6/ml). As such, it is surprising that any pregnancies were achieved.

Specifically with respect to claims 3-7, there is no description in the combination of references with respect to any sperm cells obtained from any source other than bull. As such, the combination of references does not provide any details at all as to how to make or use frozen selected equine sperm cells or frozen selected porcine sperm cells as claimed.

With respect to claim 8, the combination of references provides no description with regard to freezing sperm selected by flow cytometry at all. Limiting any description to killing flow sorted sperm by cavitation to harvest the resultant membranes and proteins.

Because the references in the combination of Salisbury et al. in view of Spaulding do not provide the requisite expectation of success at the time the invention was made a prima facie case of obviousness cannot be established with regard to the claim limitations in claim 1, nor any claim depending there from. § 2143.03, MPEP; In re Fine, 837 F.2d 1071 (Fed. Cir. 1988).

As such, appellant respectfully requests that the examiners rejection of claims 1-27 and 35 be reversed and claims 1-26 and 35 be allowed as originally recited, or as amended to further clarify fertile sperm cells.

In addition to the arguments set forth above concerning the failure to make the prima facie case of obviousness, the invention also provides unexpected advantages as compared to the combination of references cited by the examiner. Evidence of unexpected advantageous properties can rebut a prima facie case of obviousness. §716.02(a), MPEP; In Re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1986).

As indicated by the Salisbury reference the only test that can predict how well the genetic material of sperm cells is maintained by a process is use. Salisbury at page 442.

The "ultimate test of a procedure is fertility. . .." Salisbury at page 534. This is true because "the exact nature of total freeze-thaw damage is not fully understood." Salisbury at page 497. Reports of superior survival and fertility in other extenders are numerous, but possible interactions with other factors in seminal processing make it impossible to generalize these findings; a satisfactory extender for one animal or one set of conditions may not be acceptable for others. Salisbury at page 499.

As can be understood from scrutinizing the combination of references, there is no showing of any use of any selected frozen sperm cells sufficient under the test of Salisbury to prove fertility of any type of selected frozen sperm cells. No frozen selected sperm cell has been shown by the combination of references to actually achieve fertilization of even a single egg of any kind female mammal, whether in vitro or in vivo.

Even with respect to the selected sperm cells modified as described in the Spaulding reference (col. 18, lines 14-56), which are not treated in accordance with any embodiment of the invention, but rather involved neat semen into which antibodies were mixed, there is not a single example of actually achieving even a single fertilization of any egg of any kind of female mammal whether in vitro or in vivo to show that frozen selected sperm cells (those with antibodies attached) were fertile upon thawing.

By comparison, as discussed above in appellant's discussion of the breadth of the term "sperm", and as described by the 11 field trials set out in the specification (page 45, line 2) the main objective was to determine fertility of frozen selected sperm processed in

accordance with the various embodiments of the invention. Specification at page 41, starting at line 7. The pregnancy rates in accordance with embodiments of the invention were 49.0% with 203 pregnancies overall. Specification page 45, lines 19-20.

Moreover, the specification provides evidence that these pregnancies were actually accomplished by the selected sperm cells. In those trials with frozen flow sorted selected sperm cells, the subject matter of claim 8, "where the objective was to obtain female offspring, except in trial 8, accuracy was 95%, 83%, 90%, 82%, and 94%. . .respectively. Specification page 45, lines 27-28.

These results evidence a successful test as set out by Salisbury showing that the "frozen selected sperm cells" made in accordance with the invention are fertile. Salisbury at page 442.

"This result surprising because of the well-documented fragility of sperm" as set out in the appellants specification (Specification for example at pages 3, lines 13 -14; page 1, lines 28-31; page2, line 1, page 2, lines 3-4; page 2, lines 15-17; page 6, lines 21-27) and the combination of references provided by the office (Salisbury for example at pages 444, 445, 445, and 446); the scientific understanding prior to the invention as set out in the Offices own combined citations which shows that "the exact nature of total freeze-thaw damage is not fully understood" and that "it is impossible" to generalize one set of conditions for freezing sperm cells to a novel set of circumstances (Salisbury at pages 497 and 499); and the failure of others, including but not limited to those inventors

and investigators in the combination of references provided by the Office, to make the showing first.

The appellants have demonstrated for the first time that pregnancies can be achieved with sperm that has been selected and then frozen. Appellants have provided by comparison to the combination of references provided by the Office, evidence of a benefit not obtained prior to the invention itself; showing that the frozen selected sperm cells which are the subject matter of claim 1 are fertile selected sperm cells capable of fertilizing an egg of a female mammal and achieving pregnancies.

Because appellant has shown an unexpected advantage over the art, appellant respectfully requests that the examiner's rejection of claims 1-27 and 35 be reversed, and the claims allowed as originally recited, or amended to clarify the sperm cells are fertile.

SUMMARY

For the foregoing reasons, it is submitted that the examiner's rejections of claims 1-26 and 35 were erroneous, and reversal of his decision is respectfully requested.

Dated this 7 day of October 2002.

Respectfully Submitted,
SANTANGELO LAW OFFICES, P.C.

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APPENDIX A
CLAIMS 1-37 AS ORIGINALLY FILED

1. A method for the cryopreservation of sperm comprising:

(a) obtaining a selected sperm sample;

(b) cooling said selected sperm sample;

(c) isolating sperm from said selected sperm sample to produce isolated sperm;

(d) adding final extender to said isolated sperm to produce a suspension of sperm; and

(e) freezing said suspension of sperm.

2. The method of Claim 1 wherein said selected sperm sample comprises a portion of the sperm present in a source sample, said portion of sperm selected for a characteristic, and wherein the sperm concentration in the selected sperm sample is lower than in the source sample.

3. The method of Claim 1 wherein said selected sperm sample comprises sex-selected sperm.

4. The method of Claim 1 wherein said selected sperm sample comprises mammalian sperm.

5. The method of Claim 1 wherein said selected sperm sample comprises bovine sperm.

6. The method of Claim 1 wherein said selected sperm sample comprises equine sperm.

7. The method of Claim 1 wherein said selected sperm sample comprises porcine sperm.

8. The method of Claim 1 wherein said selected sperm sample comprises sperm selected by a method from the group consisting of flow cytometry, a magnetic technique, a columnar technique, a gravimetric technique, a biomedical technique, a technique based on motility of sperm, a technique based on an electrical property of sperm, and any combination thereof.

9. The method of Claim 8 wherein sperm have been selected by flow cytometry.

10. The method of Claim 1 wherein cooling is carried out by reducing the temperature of the selected sperm sample to about 5°Celsius.

11. The method of Claim 10 wherein cooling is carried out over a period of about 60 minutes to about 240 minutes.

12. The method of Claim 1 wherein the final extender added to said selected sperm sample each comprise, in addition to cryoprotectant, one or more of the following components: a component that maintains osmolality and buffers pH, an organic substance that reduces cold shock and preserves fertility of sperm, an energy source, a substance that facilitates sperm capacitation, and an antibiotic.

13. The method of Claim 12 wherein said cryprotectant is selected from the group consisting of disaccharides, trisaccharides, and any conbination thereof.

14. The method of Claim 12 wherein said cryoprotectant is selected from the group consisting of glycerol, dimethyl sulfoxide, ethylene glycol, propylene glycol, and any combination thereof.

15. The method of Claim 12 wherein said component that maintains osmolality and buffers pH is selected from the group consisting of a buffer comprising a salt, a buffer containing a carbohydrate, and any combination thereof.

16. The method of Claim 12 wherein said component that maintains osmolality and buffers pH is selected from the group consisting of sodium citrate, Tris{hydroxymethyl]aminomethane, N-Tris]hydroxymethyl]methyl-2-aminoethanesulfonic acid, monosodium glutamate, milk, HEPES buffered medium, and any combination thereof.

17. The method of Claim 12 wherein said organic substance is selected from the group consisting of egg yolk, an egg yolk extract, milk, a milk extract, casein, albumin, lecithin, and any combination thereof.

18. The method of Claim 12 wherein said energy source is a monosaccharide selected from the group consisting of glucose, fructose, mannose, and any combination thereof.

19. The method of Claim 12 wherein said antibiotic is selected from the group consisting of tylosin, gentamicin, lincomycin, linco-spectin, spectinomycin, penicillin, streptomycin, and any combination thereof.

20. The method of Claim 1 wherein, after the addition of the final extender the sperm sample and suspension of sperm, respectively, comprise glycerol, sodium citrate, Tris[hydroxymethyl]aminomethane, egg yolk, fructose, and one or more antibiotics.

21. The method of Claim 1 wherein, after the addition of the final extender said sperm sample and suspension of sperm, each comprise glycerol, sodium citrate, egg yolk, and one or more antibiotics.

22. The method of Claim 1 wherein, after the addition of the final extender said sperm sample and suspension of sperm, each comprise glycerol, egg yolk, milk, fructose, and one or more antibiotics.

23. The method of Claim 1 wherein said extender has a pH in the range of about 6.5 to about 7.5.

24. The method of Claim 1 wherein the sperm are isolated from said selected sperm sample by centrifugation.

25. The method of Claim 24 wherein said centrifugation allows for at least about 50% to about 90% recovery of sperm.

26. The method of Claim 1 wherein the concentration of sperm in said suspension prior to freezing is about 1 x 10^6/ml to about 300 x 10^6/ml.

27. A frozen selected sperm sample comprising portion of the sperm present in a source sample, said portion of sperm selected for a characteristic.

28. The frozen selected sperm sample of Claim 27 wherein said frozen selected sperm sample comprises sex-selected sperm.

29. The frozen selected sperm sample of Claim 27 wherein said frozen selected sperm sample comprises mammalian sperm.

30. The frozen selected sperm sample of Claim 29 wherein said frozen selected sperm sample comprises bovine sperm.

31. The frozen selected sperm sample of Claim 29 wherein said frozen selected sperm sample comprises equine sperm.

32. The frozen selected sperm sample of Claim 29 wherein frozen selected sperm sample comprises porcine sperm.

33. The frozen selected sperm sample of Claim 27 wherein the method used to select said selected sperm sample comprises a technique, a columnar technique, a gravimetric technique, a biochemical technique, a technique based on motality of sperm, a technique based on an electrical property of sperm, and any combination thereof.

34. The frozen selected sperm sample of Claim 33 wherein said frozen selected sperm sample comprises sperm that have been selected by flow cytometry.

35. The frozen selected sperm sample of Claim 27 wherein said frozen selected sperm sample is produced by a method comprising:

(a) obtaining a selected sperm sample;

(b) cooling said selected sperm sample;

(c) isolating sperm from said selected sperm sample to produce isolated sperm;

(d) adding final extender to said isolated sperm to produce a suspension of sperm; and

(e) freezing said suspension of sperm.

36. A method comprising using the frozen selected sperm sample of Claim 27 for artificial insemination or in vitro fertilization.

37. The method of Claim 36 comprising using frozen selected sperm sample for low-dose artificial insemination.

EXHIBIT B

ELECTED CLAIMS IN GROUP I (1-26 AND 35)

1. A method for the cryopreservation of sperm comprising:

(a) obtaining a selected sperm sample;

(b) cooling said selected sperm sample;

(c) isolating sperm from said selected sperm sample to produce isolated sperm;

(d) adding final extender to said isolated sperm to produce a suspension of sperm; and

(e) freezing said suspension of sperm.

2. The method of Claim 1 wherein said selected sperm sample comprises a portion of the sperm present in a source sample, said portion of sperm selected for a characteristic, and wherein the sperm concentration in the selected sperm sample is lower than in the source sample.

3. The method of Claim 1 wherein said selected sperm sample comprises sex-selected sperm.

4. The method of Claim 1 wherein said selected sperm sample comprises mammalian sperm.

5. The method of Claim 1 wherein said selected sperm sample comprises bovine sperm.

6. The method of Claim 1 wherein said selected sperm sample comprises equine sperm.

7. The method of Claim 1 wherein said selected sperm sample comprises porcine sperm.

8. The method of Claim 1 wherein said selected sperm sample comprises sperm selected by a method from the group consisting of flow cytometry, a magnetic technique, a columnar technique, a gravimetric technique, a biomedical technique, a technique based on motility of sperm, a technique based on an electrical property of sperm, and any combination thereof.

9. The method of Claim 8 wherein sperm have been selected by flow cytometry.

10. The method of Claim 1 wherein cooling is carried out by reducing the temperature of the selected sperm sample to about 5°Celsius.

11. The method of Claim 10 wherein cooling is carried out over a period of about 60 minutes to about 240 minutes.

12. The method of Claim 1 wherein the final extender added to said selected sperm sample each comprise, in addition to cryoprotectant, one or more of the following components: a component that maintains osmolality and buffers pH, an organic substance that reduces cold shock and preserves fertility of sperm, an energy source, a substance that facilitates sperm capacitation, and an antibiotic.

13. The method of Claim 12 wherein said cryprotectant is selected from the group consisting of disaccharides, trisaccharides, and any combination thereof.

14. The method of Claim 12 wherein said cryoprotectant is selected from the group consisting of glycerol, dimethyl sulfoxide, ethylene glycol, propylene glycol, and any combination thereof.

15. The method of Claim 12 wherein said component that maintains osmolality and buffers pH is selected from the group consisting of a buffer comprising a salt, a buffer containing a carbohydrate, and any combination thereof.

16. The method of Claim 12 wherein said component that maintains osmolality and buffers pH is selected from the group consisting of sodium citrate, Tris{hydroxymethyl]aminomethane, N-Tris]hydroxymethyl]methyl-2-aminoethanesulfonic acid, monosodium glutamate, milk, HEPES buffered medium, and any combination thereof.

17. The method of Claim 12 wherein said organic substance is selected from the group consisting of egg yolk, an egg yolk extract, milk, a milk extract, casein, albumin, lecithin, and any combination thereof.

18. The method of Claim 12 wherein said energy source is a monosaccharide selected from the group consisting of glucose, fructose, mannose, and any combination thereof.

19. The method of Claim 12 wherein said antibiotic is selected from the group consisting of tylosin, gentamicin, lincomycin, linco-spectin, spectinomycin, penicillin, streptomycin, and any combination thereof.

20. The method of Claim 1 wherein, after the addition of the final extender the sperm sample and suspension of sperm, respectively, comprise glycerol, sodium citrate, Tris[hydroxymethyl]aminomethane, egg yolk, fructose, and one or more antibiotics.

21. The method of Claim 1 wherein, after the addition of the final extender said sperm sample and suspension of sperm, each comprise glycerol, sodium citrate, egg yolk, and one or more antibiotics.

22. The method of Claim 1 wherein, after the addition of the final extender said sperm sample and suspension of sperm, each comprise glycerol, egg yolk, milk, fructose, and one or more antibiotics.

23. The method of Claim 1 wherein said extender has a pH in the range of about 6.5 to about 7.5.

24. The method of Claim 1 wherein the sperm are isolated from said selected sperm sample by centrifugation.

25. The method of Claim 24 wherein said centrifugation allows for at least about 50% to about 90% recovery of sperm.

26. The method of Claim 1 wherein the concentration of sperm in said suspension prior to freezing is about 1 x 10^6/ml to about 300 x 10^6/ml.

35. The frozen selected sperm sample of Claim 27 wherein said frozen selected sperm sample is produced by a method comprising:

(a) obtaining a selected sperm sample;

(b) cooling said selected sperm sample;

(c) isolating sperm from said selected sperm sample to produce isolated sperm;

(d) adding final extender to said isolated sperm to produce a suspension of sperm; and

(e) freezing said suspension of sperm.